

# Assessment of Glomerular Filtration Rate Measurement and Estimation Methods in the Evaluation of CKD

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## Abstract

Glomerular filtration rate (GFR) is the principal indicator used to evaluate renal function and to diagnose, stage, and monitor chronic kidney disease (CKD). Although direct determination of GFR through renal clearance techniques remains the reference approach, routine clinical implementation is constrained by procedural complexity, cost, and limited accessibility. Inulin clearance continues to serve as the benchmark method because of its ideal physiological characteristics; however, its practical limitations have encouraged the adoption of alternative approaches. Creatinine clearance is commonly employed owing to its convenience, yet tubular secretion of creatinine frequently leads to overestimation of true filtration capacity. Pharmacological inhibition of creatinine secretion with cimetidine can improve the accuracy of creatinine clearance measurements under appropriate clinical conditions. Estimation equations derived from serum creatinine, including pediatric formulas, provide a practical means of assessing kidney function, although their performance may vary depending on assay standardization and patient characteristics. Cystatin C has emerged as a promising endogenous biomarker because its production is relatively stable and less affected by muscle mass, making it particularly valuable for identifying mild reductions in kidney function. Nevertheless, additional evidence is required to establish its optimal role across diverse patient populations. Among exogenous filtration markers, plasma clearance techniques using iohexol have demonstrated excellent agreement with established reference methods while offering greater feasibility for clinical and research applications. Evidence from pediatric CKD investigations indicates that iohexol-based plasma disappearance protocols employing either multiple or simplified sampling schedules provide reliable and reproducible GFR measurements. Continued refinement of both measured and estimated GFR methodologies is expected to enhance the accuracy of kidney function assessment and improve clinical decision-making in individuals with chronic kidney disease.

**Keywords:** Chronic kidney disease; Glomerular filtration rate; Estimated GFR; Measured GFR; Creatinine clearance; Serum creatinine; Cystatin C; Iohexol clearance; Renal function assessment; kidney disease biomarkers.

## Introduction

Glomerular filtration rate (GFR) represents the volume of plasma filtered by the glomeruli each minute and is widely accepted as the most reliable overall indicator of kidney function (1). The filtration process depends on the structural integrity of the

glomerular filtration barrier, renal blood flow, hydrostatic pressure within the glomerular capillaries, and oncotic pressure generated by plasma proteins. Under normal physiological conditions, these factors maintain a stable filtration rate that supports electrolyte balance, acid-base homeostasis, and elimination of metabolic waste products (2).

In chronic kidney disease (CKD), progressive nephron loss results in adaptive hyperfiltration within the remaining nephrons. Although this compensatory response initially preserves total kidney function, sustained hyperfiltration eventually contributes to glomerular injury, sclerosis, and further nephron depletion. Consequently, GFR gradually declines as CKD advances through its clinical stages. Since structural kidney damage may occur before substantial changes in serum creatinine become evident, accurate assessment of GFR is essential for early diagnosis, disease staging, therapeutic planning, and monitoring disease progression (3) (Table 1).

### Direct Measurement Techniques for Glomerular Filtration Rate

Direct measurement of GFR relies on filtration markers that are freely filtered by the glomerulus without tubular secretion, reabsorption, metabolism, or extrarenal elimination. Inulin clearance remains the reference standard because its physiological characteristics closely match these ideal requirements. Nevertheless, the procedure requires continuous intravenous infusion, repeated blood and urine collection, and specialized laboratory analysis, making it impractical for routine clinical practice (4).

Several exogenous filtration markers have therefore been introduced as practical alternatives. These include iothexol, iothalamate, chromium-51 ethylenediaminetetraacetic acid (51Cr-EDTA), and technetium-99m diethylenetriamine pentaacetic acid (99mTc-DTPA). Plasma clearance methods based on iothexol have gained increasing acceptance because they provide high analytical accuracy while avoiding the use of radioactive substances. Simplified sampling strategies requiring only two or four blood specimens have demonstrated excellent agreement with conventional clearance techniques, facilitating their use in both research studies and specialized nephrology practice (5).

Although measured GFR remains the preferred approach when highly accurate kidney function assessment is required, its relatively high cost, technical demands, and limited availability continue to restrict widespread implementation (6).

### Estimated Glomerular Filtration Rate Using Endogenous Biomarkers

Estimated GFR (eGFR) provides a practical alternative to direct measurement and is routinely employed in clinical care. Most estimation equations utilize serum creatinine because it is inexpensive, standardized, and readily available. However, creatinine concentration is influenced by several non-renal variables, including muscle mass, age, sex, dietary protein intake, and certain medications. Consequently, creatinine-based equations may underestimate or overestimate true kidney function in selected patient populations (7).

Pediatric assessment commonly relies on the Schwartz equation, whereas adults are frequently evaluated using standardized equations developed from large clinical cohorts. Continuous refinement of estimation models has improved agreement with measured GFR by incorporating assay standardization and demographic characteristics. Despite these advances, estimated GFR should always be interpreted within the patient's overall clinical context, particularly when renal function is changing rapidly or when muscle mass differs substantially from the general population (8).

### Results and Discussion

The search for biomarkers that provide greater diagnostic accuracy has led to increased interest in cystatin C. Unlike creatinine, cystatin C is produced by all nucleated cells at a relatively constant rate and demonstrates less dependence on skeletal muscle mass or dietary intake. After glomerular filtration, it is almost completely reabsorbed and metabolized by proximal tubular cells, preventing its return to the systemic circulation (9).

Numerous investigations have demonstrated that cystatin C-based equations improve the detection of mild reductions in kidney function, particularly among elderly individuals, children, patients with reduced muscle mass, and those with chronic systemic diseases. Combining serum creatinine with cystatin C frequently produces more accurate GFR estimates than either biomarker alone (10).

| Method                    | Filtration Marker     | Advantages                              | Limitations                                | Common Clinical Use                          |
|---------------------------|-----------------------|-----------------------------------------|--------------------------------------------|----------------------------------------------|
| Inulin clearance          | Inulin                | Reference standard; highest accuracy    | Time-consuming; expensive                  | Research                                     |
| Creatinine clearance      | Endogenous creatinine | Widely available                        | Overestimates GFR due to tubular secretion | Routine evaluation                           |
| Serum creatinine eGFR     | Creatinine            | Simple; rapid                           | Influenced by muscle mass and diet         | CKD screening                                |
| Cystatin C eGFR           | Cystatin C            | Better sensitivity in selected patients | Higher laboratory cost                     | Confirmatory assessment                      |
| Iothexol plasma clearance | Iothexol              | High accuracy; non-radioactive          | Specialized laboratory required            | Clinical research and specialized nephrology |

Table 1: Comparison of Common Methods Used for GFR Assessment

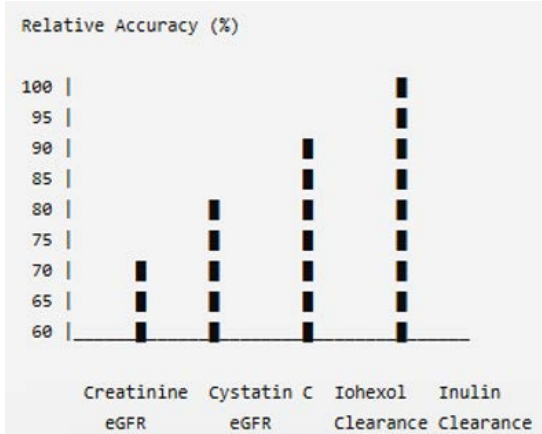


**Figure 1:** Comparison of Relative Accuracy of Common GFR Assessment Methods

Recent developments in laboratory medicine have also focused on integrating artificial intelligence, machine learning algorithms, and multimarker prediction models to improve kidney function estimation. These approaches may enhance diagnostic precision and facilitate personalized assessment in future nephrology practice (11) (Figure 1).

## Clinical Applications and Future Perspectives

Reliable assessment of GFR plays a central role throughout the management of chronic kidney disease. Kidney function measurements guide disease staging, medication dose adjustment, referral for specialist care, dialysis planning, and evaluation of kidney transplant candidates. Regular monitoring also enables clinicians to identify progressive decline, assess treatment effectiveness, and recognize acute deterioration superimposed on chronic disease (12).

Selection of an appropriate GFR assessment method should consider clinical objectives, patient characteristics, available resources, and required measurement precision. Estimated GFR remains sufficient for routine outpatient management, whereas measured GFR is recommended when precise kidney function evaluation is necessary, including research studies, living kidney donor assessment, and administration of potentially nephrotoxic therapies (13).

Future research should prioritize validation of emerging biomarkers, development of population-specific estimation equations, integration of digital health technologies, and harmonization of laboratory methods. These advances have the potential to improve early detection of CKD and optimize long-term patient outcomes (14).

## Conclusion

Accurate assessment of glomerular filtration rate remains central to the diagnosis, staging, and management of chronic

kidney disease, with the choice of method depending on the balance between precision and practicality. While inulin clearance continues to serve as the reference standard and exogenous markers such as iohexol offer excellent accuracy with greater clinical feasibility, these direct measurement techniques remain limited by cost, complexity, and restricted availability. Consequently, estimated GFR based on endogenous biomarkers—particularly serum creatinine, and increasingly cystatin C—remains the practical mainstay for routine clinical evaluation, despite being influenced by non-renal factors such as muscle mass, age, and diet. As estimation equations continue to be refined and emerging tools such as multimarker panels and artificial intelligence-based models are integrated into practice, the accuracy and personalization of kidney function assessment are expected to improve, ultimately supporting earlier detection of CKD, more precise disease monitoring, and better long-term patient outcomes.

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